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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 11/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,006	SCHINDLER, HANSGEORG	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-45 and 61* is/are pending in the application.

4a) Of the above claim(s) *41 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-40, 42, 44, 45 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed June 27, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 24-45 and 61 were pending. Claims 24-45 and 61 have been amended. No claims were added or canceled. Therefore, claims 24-45 and 61 are currently pending.

4. Claims 41 and 43 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

5. Therefore, claims 24-40, 42, 44, 45 and 61 are examined on the merits in this action.

Withdrawn Objections/Rejections

6. The rejection denoted "G" under 35 U.S.C. § 112, second paragraph is withdrawn in view of Applicant's arguments and/or amendments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 101

7. Claim 25 is rejected under 35 U.S.C. 101 because the claim is directed to non-statutory subject matter. Independent claim 24 is drawn to an apparatus "for visualizing molecules" and dependent claim 25 further comprises a product described as "biological cells" which are placed into said apparatus (e.g., see claim 25; see also Applicants' 7/26/04 arguments, page 8, first full paragraph). Thus, claim 25 is drawn to two statutory classes of invention (i.e., a product and an apparatus), rather than a single statutory class of invention. This is not permissible. For example, see MPEP § 2173.05(p), "Such claims should ... be rejected under 35 U.S.C. 101 based on the theory that the claim ... embraces or overlaps two different statutory classes of invention set forth in 35 U.S.C. 101 which is drafted so as to set forth the statutory classes of invention in the alternative only" (emphasis added).

The Examiner concedes that there are situations where claims are permissively drafted to include a reference to more than one statutory class of invention (e.g., see MPEP § 2173.05(p) disclosing "product-by-process" claims), but the Examiner notes that those situations are only permissible because Applicants make clear that the "product" and NOT the "process" is being claimed (e.g., see MPEP § 2173.05(p), "A claim to a device, apparatus, manufacture, or composition of matter may contain a reference to the process in which it is intended to be used without being objectionable under 35 U.S.C. 112, second paragraph, so long as it is clear that the claim is directed to the product and not the process") (emphasis added). Here, it would appear that both the "apparatus" and the "product" are simultaneously being claimed (e.g., see Applicant's 7/26/04 Response, page 8, first full paragraph).

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 101 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons.

Applicant argues, "The embodiment claimed in claim 25 is specifically one in which the claimed arrangement further comprises the additional limitation of biological cells in the sample holder. Applicant is claiming this apparatus, and is not attempting to claim the biological cells by themselves" (e.g., 6/27/05 Response, page 10, section D).

This is not found persuasive for the following reasons:

Although Applicant's position is not entirely clear, the Examiner maintains that Applicants are trying to claim a non-statutory class of invention as set forth in the rejection above. Contrary to Applicant's assertions, the Examiner has never stated that the biological cells "by themselves" violated 35 U.S.C. § 101. Rather, the "combination" of the apparatus and the cells violates the provision as two statutory classes of invention are impermissibly encompassed by the claim (i.e., apparatus + product).

Accordingly, the 35 U.S.C. § 101 rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 112, second paragraph

9. Claims 24-40, 42, 44, 45 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

AA. ***Claim 25*** is indefinite because Applicant is claiming more than one statutory class of invention in the same claim. For example, Applicants state in their 7/26/04 Response, "... [claim 25] requires that biological cells be present in the sample holder .... further limit[ing] claim 24" (e.g., see 7/26/04 Response, page 8, first full paragraph). Thus, Applicants are clearly trying to claim both a "product" (i.e., the biological cells) and an "apparatus" (i.e., the arrangement adapted for the visualization of said cells) in the same claim. This is not permissible (e.g., see *In Ex parte Lyell* wherein the Court struck down a claim drawn to two statutory classes of invention, 17 USPQ2d 1548 (Bd. Pat. App. & Inter. 1990) (a claim directed to an automatic transmission workstand and the method steps of using it was held to be ambiguous and properly rejected under 35 U.S.C. 112, second paragraph). See more generally MPEP § 2173.05(p).

Please note that other "statutory hybrid" claims are not rejected like product-by process claims because Applicants make clear what is being claimed i.e., the product and NOT the process (see MPEP § 2173.05(p), "A claim to a device, apparatus, manufacture, or composition of matter may contain a reference to the process in which it is intended to be used without being objectionable under 35 U.S.C. 112, second paragraph, so long as it is clear that the claim is directed to the product and not the process") (emphasis added). That is not the case here. To the contrary, Applicants have made it clear that both the "apparatus" and the "product" are being claimed simultaneously (e.g., see 7/26/04 Response, page 8, first full paragraph).

BB. ***Claim 24*** recites "large-area" fluorescence excitation. The term "large-area" is a relative term, which renders the claim indefinite and/or unclear. The term is not defined

by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b). The Examiner notes that Applicant's specification states, "Due to the large-area fluorescence excitation, preferably 100 to 10,000 μm^2, depending on the application, imaging of the excited molecules may be very rapid" (see page 7, paragraph 2). However, this statement is merely exemplary in nature and does not further limit the term "large" to a range from 100 to 10,000 μm^2 and, as a result, it is not clear to what extent the term "large" could extend beyond this limit (e.g., would 90 μm^2 infringe, 80 μm^2 infringe, etc). Thus, the metes and bounds of the claimed invention cannot be determined. Therefore, claim 24 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Response

10. Applicant's arguments directed to the above 35 U.S.C. 112, second paragraph rejection denoted BB were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons.

BB. Applicant argues, "... According to the Sonnleitner Declaration ... the term 'large-area fluorescent excitation' as used in claim 24 is synonymous with the term 'wide-field' microscopy ... Therefore, the definitional and practical distinctions detailed in the Peter J. Shaw reference cited in the 7/26/054 Response apply equally to 'wide-field microscopy' [presumably even though the Shaw reference never mentions the term]"

(e.g., see 6/27/05 Response, pages 8-10; see also Appendix A, Declaration of Dr. Max Sonnleitner under 37 C.F.R. § 1.132).

This is not found persuasive for the following reasons:

The Examiner respectfully disagrees. Sonnleitner's Declaration outlines the differences between wide-field microscopy (which is not currently claimed) and confocal microscopy. The only reference to large-area fluorescent excitation (which is currently claimed) is an unsupported statement that large-area fluorescent has the same meaning as wide-field illumination as used in Applicant's specification and claims (e.g., see Sonnleitner 37 C.F.R. § 1.132 Declaration, pages 1-3, especially, page 2, section 3, "The term 'large-area fluorescent excitation' as used in the specification and claims has the same meaning to one of skill in the filed of fluorescence microscopy as the term 'wide-field' illumination"). This is not persuasive. If these two terms (i.e., large-area fluorescent excitation and wide-field illumination) possess the exact same meaning as alleged by Dr. Sonnleitner, then the Declarent should have had no trouble documenting this assertion or pointing to pertinent portions of the specification that support this conclusion. This has not been done. Likewise, Applicant has similarly failed to provide a reference that sets forth a definition for the currently claimed large-area fluorescent excitation. As previously stated, the Peter J. Shaw reference set forth by Applicant never mentions the term (e.g., reference to large-are fluorescent excitation in the quoted paragraph on page 9 of the 6/27/05 response was added by Applicant and not the original reference). In addition, the specification never mentions that large-area fluorescent

excitation is a substitute for wide-field microscopy. Therefore, Applicant's position is not supported in fact.

Claims Rejections - 35 U.S.C. 102

11. Claims 24-28, 30-34 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Sharonov et al. (Sharonov, S.; Chourpa, I.; Morjani, H.; Nabiev, I.; Manfait, M. "Confocal spectral imagining analysis in studies of the spatial distribution of antitumor drugs within living cancer cells" *Analytica Chimica Acta* **1994**, *290*, 40-47) (of record).

For ***claims 24 and 61***, Sharonov et al. (see entire document) disclose an apparatus for confocal spectral imaging analysis (e.g., see Sharonov et al, abstract; see also figure 2), which anticipates claims 24 and 61. For example, Sharonov et al. disclose at least one source of light adapted to fluorescently excite, via single or multiple photon absorption marker molecules in said sample (e.g., see figure 2, element 1 wherein a Spectra-Physics Model 2026 laser is disclosed as the light source; see also abstract wherein both bound and unbound doxorubicin and mitroxantrone are disclosed and the marker molecules inside the K562 cancer cells; see also figures 4-5). Sharonov et al. do not explicitly state that the light source is adapted for large-area fluorescent excitation, but the Examiner contends that this would be an inherent property of the laser because Applicants' most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see specification, page 7, middle paragraph, "only the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser"; see also claim 34) (emphasis added). Moreover, Sharonov et al. disclose the excitation of a 20 ×

20 μm region = 400 μm^2 (e.g., see Sharonov et al., page 42, column 1, last paragraph), which falls within Applicants' most preferred range of 100 to 10,000 μm^2 (e.g., see specification, page 7, middle paragraph, "the large-area fluorescence excitation, preferably 100 to 10,000 μm^2, depending on the application"; see also 35 U.S.C. § 112, second paragraph rejection below), which is between 100 to 10,000 μm^2. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, Sharonov et al. disclose a sample holder (e.g., see figure 2, element 5). Sharonov et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see figure 2, element 8). Sharonov et al. also disclose a detection and analysis system and a sample holder that are movable laterally relative to each other during use (e.g., see figure 2, elements 2 and 6; see also page 42, last paragraph, "The sample compartment is moved with an automatic scanning stage ... and can be scanned along the y-axis [i.e., laterally] with a minimum step size of 0.1 um. The scanning of the sample along the x-axis is achieved by the optical scanner being installed in the confocal entrance chamber"). Sharonov et al. also disclose a control unit

that is adapted to coordinate and synchronize illumination times and lateral movement between said sample holder and said detection and analysis system (e.g., see figure 2, elements 6 and 9; see also page 42, column 1, paragraph 2 wherein an IBM PC/AT-486 is disclosed, "The scanning of the sample stage and mirrors of the optical scanner and all operations connected with recording of spectra are computer-controlled (IBM PC/AT-486) by the ImageSoft software through the net-work between the IBM PC/AT and the RISC 6000 work station"; see also page 42, column 2, paragraphs 2-5; see also figure 3).

Sharonov et al. do not explicitly state that said arrangement has been "adapted" to visualize movements of molecules, interactions between molecules, and molecular processes in a sample during use, by using a single dye tracing (SDT) method. However, the Examiner contends that Sharonov et al. inherently discloses this limitation (e.g., see Sharonov et al., abstract and figure 4). For example, the experimental set up in Sharonov et al. was "adapted" to visualize living cancer cells treated with the fluorescent antitumour drugs doxorubicin and mitroxantrone (e.g., see abstract). Thus, Sharonov et al. teach visualization of the movements of molecules (e.g., see Sharonov et al., page 47, "Direct express imaging of drug deposits within cells will be helpful in analyzing the accumulation [i.e., movement], distribution and efflux of the drugs"), interactions between molecules (e.g., see Sharonov et al., page, 44, paragraph bridging columns 1-2, "The fluorescence spectrum of the drug-DNA complex is changed as compared with the free drug") and molecular process in a sample during use (e.g., see page 44, paragraph bridging columns 1-2, see also figures 3-5). Furthermore, Sharonov et al. disclose the use of a "single dye" such as mitroxantrone (e.g., see figure 4) or doxorubicin (e.g., see figure

5) in each experiment. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, the Examiner argues in the alternative that Applicants' "adaptation" element (i.e., see claim 24, last three lines) represents "intended use" language and thus is not afforded any patentable weight. Claims directed to apparatus must be distinguished from the prior art in terms of structure rather than function (e.g., see *In re Danly*, 263 F.2d 844, 847, 120 USPQ 528, 531 (CCPA 1959). "[A]pparatus claims cover what a device is, not what a device does." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990). (emphasis in original). A claim containing a "recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art apparatus" if the prior art apparatus teaches all the structural limitations of the claim. Ex parte Masham, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicant's claim language only sets forth what the apparatus does (i.e., adapted to visualize movements of molecules ... using a single dye tracing (SDT) method) rather than what it is (i.e., describe a structural limitation) and, as a result, fails to distinguish the claimed apparatus

from the prior art in terms of its structure. Furthermore, it is even if *assuming arguendo* this "adaptation" is to be afforded patentable weight, the Examiner contends that the metes and bounds of the claimed invention cannot be determined (e.g., see 35 U.S.C. § 112, second paragraph below).

For ***claim 25***, Sharonov et al. disclose an apparatus that can visualize interactions between molecules and molecular processes in biological cells (e.g., see figure 4, especially figure 4c-d wherein drug binding interactions were demonstrated for mitroxantrone in the nuclear inclusions).

For ***claim 26***, Sharonov et al. disclose "the same" marker molecules (e.g., see figure 4 wherein mitroxantrone is shown in both the nuclear membrane and in the cytoplasm, DNA-bound mitroxantrone is also shown; see also maintained 35 U.S.C. 112, second paragraph rejection).

For ***claim 27***, Sharonov et al. disclose different marker molecules (e.g., see figure 4 wherein both "bound" and "unbound" mitroxantrone are shown; compare also figures 4-5 wherein both doxorubicin and mitroxantrone are used; see also figure 1; see also maintained 35 U.S.C. 112, second paragraph rejection).

For ***claim 28***, Sharonov et al. disclose adjusting the wavelength during use from 457.9 to 514.5 nm (e.g., see page 42, column 2, paragraph 1).

For ***claim 30***, Sharonov et al. disclose 20 $\mu m \times 20\ \mu m = 400\ \mu m^2$ (e.g., see Sharonov et al., page 42, column 1, last paragraph).

For ***claim 31***, Sharonov et al. disclose a control unit that is adapted to coordinate and synchronize positioning and shifting of images to each sample position on a pixel

array of said CCD camera (e.g., see page 41, column 2, second to last paragraph; see also page 42, column 2, paragraphs 2-3; see also page 43, column 1, paragraph 2).

For ***claims 33-34***, Sharonov et al. disclose an acousto-optically switchable laser (e.g., see figure 2, element 1; see also page 42, paragraph bridging columns 1-2 wherein a switchable Spectra-Physics Model 2026 is disclosed).

Response

12. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicant argues, "Sharonov ... do not teach an apparatus adapted to visualize movements of molecules, nor do they teach an adaptation of the single dye tracing method ... [furthermore these limitations] are found in the body of present claim 24 rather than the preamble [and thus should be afforded patentable weight] (e.g., see 6/27/05 Response, pages 12-13).

[2] Applicant argues, "Large-Area Fluorescent Excitation is not an inherent property of a laser ... Sharonov ... do not illuminate a region at least 100 μm^2 in the same manner as applicant ... Sharonov teaches scanning a 20×20 [i.e., 400 μm^2] over the course of 10 minutes ... Sanchez [and Sharonov presumably by analogy to Sanchez, see below] is ... not illuminating the entire sample simultaneously" (e.g., see 6/27/05 Response, pages 13 and 14).

[3] Applicant argues, "Sharonov ... teach nothing about single dye tracing or large-area fluorescent microscopy" and cites the Sonnleitner Declaration is support of this position (e.g., see 6/27/05 Response, page 14; see also Sonnleitner Declaration).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Sharonov et al. inherently discloses this limitation as set forth in the newly amended rejection above or, in the alternative, this limitation does not adequately distinguish the claimed invention from the prior art because it does not set forth any structural features (e.g., see *In re Danly*, 263 F.2d 844, 847, 120 USPQ 528, 531 (CCPA 1959). "[A]pparatus claims cover what a device is, not what a device does." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990). In addition, the claimed recitation of a use (i.e., "use" of the SDT method), without setting forth any steps involved in the process (i.e., no positive method steps are set forth for the SDT method in the claim), results in an improper definition of a process (e.g., see for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966)) and, as a result, an improper definition of the apparatus that is defined (in part) by said process (e.g., see 35 U.S.C. 112, second paragraph rejection below).

[2] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (e.g., "illuminating the entire sample simultaneously") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition,

the metes and bounds of "large-area fluorescent excitation" are unclear (e.g., see 35 U.SC. 112, second paragraph rejection above).

[3] The Examiner contends that the "large-area fluorescent microscopy" limitation was adequately addressed in sections **[1 and/or 2]** above, which are incorporated in their entirety herein by reference. Furthermore, the term "large-are fluorescent microscopy" is unclear (e.g., see 35 U.S.C. 112, second paragraph rejection above, which is incorporated in its entirety herein by reference) and, as a result, Applicants' arguments are moot. In addition, the Examiner contends that Sharonov et al. inherently disclose the requisite "adaptation" as set forth in the newly amended rejection above or, in the alternative, said adaptation does not properly distinguish the claimed apparatus from the prior art (e.g., see newly amended rejection above; see also 35 U.S.C. 112, second paragraph rejection below).

Accordingly, the 35 U.S.C. §102(b) rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 102

13. Claims 24, 26, 27, 30, 32, 34, 35, 37 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Sanchez et al. (Sanchez, E. J.; Novotny, L.; Holtom, G. R.; Xie, S. "Room-Temperature Fluorescence Imaging and Spectroscopy of Single Molecules by Two-Photon Excitation" *Journal of Physical Chemistry A* **September 18, 1997**, *101(38)* 7019-7023) (10/23/03 IDS, Reference C8).

For ***claims 24***, Sanchez et al. (see entire document) disclose an apparatus for room temperature fluorescence imagining and spectroscopy of single molecules by two-photon excitation, which anticipates the claimed invention (e.g., see abstract; see also

figure 1). For example, Sanchez et al. disclose at least one source of light adapted for large-area fluorescence, via single or multiple photon absorption, of marker molecules in said sample during use (e.g., see figure 1 wherein Argon Ion laser is disclosed; see also Experimental section, paragraph 1 wherein a Ti-sapphire "two-photon" excitation laser is disclosed). Sanchez et al. do not explicitly state that the light source is adapted for large-area fluorescent excitation, but the Examiner contends that this would be an inherent property of the laser because Applicants' most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see specification, page 7, middle paragraph, "only the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser"; see also claims 32 and 34; see also page 13 of Applicant's specification wherein the method of Sanchez was disclosed as a preferred embodiment) (emphasis added). Moreover, Sanchez et al. disclose the excitation of a 10 $\times$ 10 μm^2 region = 100 μm^2 (e.g., see Sanchez et al., page 42, column 1, last paragraph), which falls within Applicants' most preferred range of 100 to 10,000 μm^2 (e.g., see specification, page 7, middle paragraph, "the large-area fluorescence excitation, preferably 100 to 10,000 μm^2, depending on the application"; see also 35 U.S.C. § 112, second paragraph rejection below). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO

Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, Sanchez et al. disclose a sample holder (e.g., see figure 1 wherein the sample holder is labeled). Sanchez et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see figure 1 wherein the CCD camera is labeled; see also page 7021, column 2, last paragraph; see also Experimental section wherein a Nikon Diaphot 300 inverted epifluorescent microscope is disclosed). Sanchez et al. disclose a detection and analysis system wherein at least one of the sample holder and the detection and analysis system is moveable laterally, relative to the other during use (e.g., see figure 1 wherein XY scanbed is disclosed). Finally, Sanchez et al. disclose a control unit adapted to coordinate and synchronize illumination times and lateral movement between said sample holder and said detection and analysis system during use (e.g., see Experimental Section, last paragraph, wherein "a modified Nanoscope IIIA controller was used for controlling the scan bed and image acquisition"; see also figure 1).

Sanchez et al. do not explicitly state that said arrangement has been "adapted" to visualize movements of molecules, interactions between molecules, and molecular processes in a sample during use, by using a single dye tracing (SDT) method. However, the Examiner contends that Sanchez et al. inherently discloses this limitation (e.g., see Sanchez et al., Results and Discussion; see also figure 2). For example, Sanchez et al. teach an arrangement that can image a single dye molecule (e.g., see Sanchez et al., abstract). Thus, Sanchez et al. teach the visualization of the movements of molecules

(e.g., see Sanchez et al., page 7020, "Each peak in Figure 2 is due to a single molecule, evidenced by the abrupt disappearance of the signal in the subsequent images [i.e., the movement of single molecules and/or lack thereof can be ascertained via subsequent images using this technique]"), interactions between molecules (e.g., see Sanchez et al., figure 2 wherein interactions between individual RHB dye molecules and individual RHB dye molecules and the substrate surface can be seen in this and subsequent images) and molecular process in a sample during use (e.g., figure 2; see also Each peak in Figure 2 is due to a single molecule ... The variation in intensities of the molecules are due to different molecular orientations"; see also page 7019, paragraph bridging columns 1-2, "There have been tremendous developments in recent years of detection, imaging and spectroscopy of single molecules ... All these advance4s have resulted in a paradigm for studying mane single molecule behaviors , e.g., translational and rotational diffusion [e.g., examples of molecular processes] ... etc."). Furthermore, Sanchez et al. disclose the use of a single dye tracing method (e.g., see Sanchez et al., abstract, "We report fluorescence imaging of single dye molecules ...")."When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the

term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, the Examiner argues in the alternative that Applicants' "adaptation" element (i.e., see claim 24, last three lines) represents "intended use" language and thus is not afforded any patentable weight. Claims directed to apparatus must be distinguished from the prior art in terms of structure rather than function (e.g., see *In re Danly*, 263 F.2d 844, 847, 120 USPQ 528, 531 (CCPA 1959). "[A]pparatus claims cover what a device is, not what a device does." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990). (emphasis in original). A claim containing a "recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art apparatus" if the prior art apparatus teaches all the structural limitations of the claim. Ex parte Masham, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicant's claim language only sets forth what the apparatus does (i.e., adapted to visualize movements of molecules ... using a single dye tracing (SDT) method) rather than what it is (i.e., describe a structural limitation) and, as a result, fails to distinguish the claimed apparatus from the prior art in terms of its structure. Furthermore, it is even if *assuming arguendo* this "adaptation" is to be afforded patentable weight, the Examiner contends that the metes and bounds of the claimed invention cannot be determined (e.g., see 35 U.S.C. § 112, second paragraph below).

For ***claim 26***, Sanchez et al. disclose, for example, "the same" RhB dye marker molecules (e.g., see Figure 2)

For ***claim 27***, Sanchez et al. disclose do not disclose the use of "different marker molecules, but this limitation has not been given any patentable weight because it represents intended use only. If the prior art structure is capable of performing the intended use, then it meets the claim. The Office does not have the facilities to make a comparison and the burden is on the applicants to establish any difference between the transducing elements of the art and the instant claims. Se In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claim 30***, Sanchez et al. disclose $10 \times 10\ \mu m = 100\ \mu m^2$ (e.g., see Sanchez et al. page 7022, column 2, paragraph 1).

For ***claims 32 and 34***, Sanchez et al. disclose, for example, an argon laser and/or a "two-photon" excitation laser (e.g., see figure 1; see also Experimental section).

For ***claim 35***, Sanchez et al. disclose a control unit that further comprises a pulse transmitter and a software adapted to control said at least one source of light and said movement of said sample holder during use (e.g., see Sanchez et al., figure 1; see also Experimental section, paragraph 3, wherein Nanoscope IIIA controller is used for "controlling the scan bed and image acquisition"; see also paragraph 1 wherein 100 fs pulses are disclosed).

For ***claim 37***, Sanchez et al. disclose an inverted epifluorescence microscope (e.g., see Experimental section).

For ***claim 61***, Sanchez et al. disclose lateral movement (e.g., see figure 1, XY scanbed).

Claim Rejections - 35 USC § 103

14. Claims 24, 26, 27, 29, 30, 32, 34, 35, 37, 44 and 61are rejected under 35 U.S.C. 103(a) as being unpatentable over Sanchez et al. (Sanchez, E. J.; Novotny, L.; Holtom, G. R.; Xie, S. "Room-Temperature Fluorescence Imaging and Spectroscopy of Single Molecules by Two-Photon Excitation" *Journal of Physical Chemistry A* **September 18, 1997**, *101(38)* 7019-7023) (10/23/03 IDS, Reference C8) and Lewis et al. (U.S. Patent No. 5,705,878) (Date of Patent is **January 6, 1998**).

For ***claims 24, 26, 27, 30, 32, 34, 35, 37 and 61***, Sanchez et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates and, as a result, renders obvious claims 24, 26, 27, 30, 32, 34, 35, 37 and 61.

The prior art teaching of Sanchez et al. differs from the claimed invention as follows:

For ***claim 29***, the prior art teachings of Sanchez et al. differ from the claimed invention by not specifically reciting the use of both horizontal (x an y direction) and vertical (z direction) control.

For ***claim 44***, the prior art teachings of Sanchez et al. differ from the claimed invention by not reciting the use of a piezo element.

However, Lewis et al. teach the following limitations that are deficient in Sanchez et al.:

For ***claim 29***, Lewis et al. (see entire document) teach that x, y and z control using an automated flat scanning stage (e.g., see Lewis et al., Summary of the Invention; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously"; see also figures 1-4).

For ***claim 44***, Lewis et al. teach the use of a piezo element (e.g., see Lewis et al., Summary of the Invention; see also figures 1, 2 and 4; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously").

It would have been obvious to one skilled in the art at the time the invention was made to use the fluorescence imaging and spectroscopy apparatus as taught by Sanchez et al. with the automated flat scanning XYZ stage as taught by Lewis et al. because Lewis et al. explicitly states that their "flat design" is "particularly well suited for ... confocal optical microscopy" (e.g., see Lewis et al., column 1, lines 11-14), which would encompass the confocal microscopy apparatus disclosed by Sanchez et al. (e.g., see Sanchez et al., Introduction). Furthermore, one of ordinary skill in the art would have been motivated to use the piezo XYZ stage disclosed by Lewis et al. because Lewis et al. explicitly state that their invention is "ideally suited for stage scanning confocal optical microscopy. Its inherent axial positioning capability provides a mechanism for optically slicing s ample in the z direction while scanning it through the confocal spot" (e.g., see Lewis et al., column 2, lines 40-45; see also paragraph bridging columns 3-4, "The

principle advantage of the present scanner over previous geometries is that the three-dimensional scanning is accomplished in a flat thin plate which can be readily placed close to a high power microscope objective"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Lewis et al. teach that their stage is compatible with all types of microscopes and especially with confocal microscopy disclosed by Sanchez (see Lewis et al., Summary of Invention; see also column 4, paragraph 1, "Since the scanner does not extend below the plane of the plate, the objective is completely free to be exchanged by the simple rotation mechanisms found in all optical microscopes").

Response

15. Applicant's arguments directed to the above Sanchez 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) rejections were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejections have been modified from their original version to more clearly address applicant's newly amended and/or added claims and/or arguments.

[1] Applicant argues, "Sanchez do not teach an apparatus adapted to visualize movements of molecules, nor do they teach an adaptation of the single dye tracing method ... [furthermore these limitations] are found in the body of present claim 24 rather than the preamble [and thus should be afforded patentable weight] (e.g., see 6/27/05 Response, pages 12-13).

[2] Applicant argues, "Large-Area Fluorescent Excitation is not an inherent property of a laser ... Sanchez ... do not illuminate a region at least 100 μm^2 in the same manner as applicant ... Sanchez discloses the excitation of a 10×10 μm region [i.e., 100 μm^2] ... Sanchez is scanning across the sample, not illuminating the entire sample simultaneously" (e.g., see 6/27/05 Response, pages 13 and 14).

[3] Applicant argues, "Sanchez teach nothing about single dye tracing or large-area fluorescent microscopy" and cites the Sonnleitner Declaration is support of this position (e.g., see 6/27/05 Response, page 14; see also Sonnleitner Declaration).

[4] Applicant argues, "It must thus follow that if claim 24 is not anticipated by Sanchez, then it cannot be obvious under Sanchez, either" and cites MPEP § 2143.03 in support of this position (e.g., see 6/27/05 Response, paragraph bridging pages 14-15).

[5] Applicant argues, "Lewis teaches nothing about single dye tracing or large-area fluorescent microscopy ... [thus] neither Sanchez nor Lewis teaches large-area fluorescent excitation and single dye tracing" (e.g., see 6/27/05 Response, pages 15-16).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Sanchez et al. inherently discloses this limitation as set forth in the newly amended rejections above or, in the alternative, this limitation does not adequately distinguish the claimed invention from the prior art because it does not set forth any structural features (e.g., see *In re Danly*, 263 F.2d 844, 847, 120 USPQ 528, 531 (CCPA 1959). "[A]pparatus claims cover what a device is, not what a device does." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990). In addition, the claimed recitation of a use (i.e., "use" of the SDT method), without setting forth any

steps involved in the process (i.e., no positive method steps are set forth for the SDT method in the claim), results in an improper definition of a process (e.g., see for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966)) and, as a result, an improper definition of the apparatus that is defined (in part) by said process (e.g., see 35 U.S.C. 112, second paragraph rejection below).

[2] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (e.g., "illuminating the entire sample simultaneously") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition, the metes and bounds of "large-area fluorescent excitation" are unclear (e.g., see 35 U.SC. 112, second paragraph rejection above).

[3] The Examiner contends that the "large-area fluorescent microscopy" limitation was adequately addressed in sections **[1 and/or 2]** above, which are incorporated in their entirety herein by reference. Furthermore, the term "large-are fluorescent microscopy" is unclear (e.g., see 35 U.S.C. 112, second paragraph rejection above, which is incorporated in its entirety herein by reference) and, as a result, Applicants' arguments are moot. In addition, Sanchez et al. do teach a single dye tracing method as set forth in the newly amended rejection above (e.g., see Sanchez et al., abstract, "We report fluorescence imaging of a single dye molecule"; see also 35 U.S.C. 112, second paragraph rejection below).

[4] Sanchez et al. anticipates the claimed invention (as set forth in the newly amended rejection above) and, as a result, Applicant's arguments are moot.

[5] In response to applicant's arguments against the Lewis reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the "large-area fluorescent excitation and single dye tracing" is taught by the combined references (e.g., see especially the newly amended Sanchez et al. 35 U.S.C. § 102(b) rejection and 35 U.S.C. 112, second paragraph rejections (which are incorporated in their entities herein by reference), which states that these limitations are anticipated, ambiguous and/or not afforded any patentable weight.

Accordingly, the Sanchez et al. 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) rejections cited above are hereby maintained.

16. Claims 24-40, 42, 44, 45 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al. (Schmidt, T. H.; Schutz, G. J.; Baumgartner, W.; Gruber, H. J.; Schindler, H. "Imaging of single molecule diffusion" PNAS 1996, 93, 2926-2929) (of record) and Lewis et al. (U.S. Patent No. 5,705,878) (Date of Patent is **January 6, 1998**) as evidenced by Schmidt et al. (Schmidt, T. H.; Hinterforfer, P.; Schnidler, H. "Microscopy for Recognition of Individual Molecules" *Laser und Optoelektronik* **1997**, *29(1)*, 56-62) (referred to herein as "Schmidt 1997") and Albertine et al. (e.g., see Albertine, K. H.; Cerasoli, F.; Gee M. H.; Ishihara, Y.; Tahamont, M. V.; Gottlieb, J. E.; Peters, S. P. "Morphological analysis of the activation of adherent neutrophils in vitro" *Tissue Cell* **1998** *20(4)*, 519-530) and Al-Ghoul et al.

(Al-Ghoul, K. J.; Costello, M. J.; "Light Microscopic Variation of Fiber Cell Size, Shape and Ordering in the Equatorial Plane of Bovine and Human Lenses" Molecular Vision 1997, 3, 2).

For ***claim 24***, Schmidt et al. (see entire document) teach a method for imaging single molecule diffusion (e.g., see Schmidt et al., abstract), which reads on the claimed invention. For example, Schmidt et al. teach the use of at least one source of light adapted for large-area fluorescent excitation, via single or multiple photon absorption, of marker molecules in said sample during use (e.g., see Schmidt et al., page 2926 wherein an argon-laser is disclosed, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"; see also figure 1). In addition, Schmidt et al. teach a sample holder (e.g., see page 2927, column 1, paragraph 2 wherein samples are immobilized on a cover-slip). Schmidt et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see Schmidt et al., page 2926 wherein an epifluorescence microscope equipped with a nitrogen-cooled CCD camera is disclosed, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"). Finally, Schmidt et al. disclose a control unit adapted to coordinate and synchronize illumination times (e.g., see Schmidt et al., page 2926-2927 wherein a CCD camera equipped with a TH512B chip is disclosed "... provid[ing] trigger pulses for the acousto-optic modulator for repeated illuminations"). Schmidt et al. also disclose an arrangement adapted to visualize movements of molecules, interactions between molecules, and molecular process in a sample during use (e.g., see Schmidt et al., abstract, "Here we provide methodology for visualization of the motion of

individual fluorescent molecules"; see also figures 1 and 3 showing interaction of individual lipid with other lipids in the membrane).

In addition, the Examiner argues in the alternative that Applicants' "adaptation" element (i.e., see claim 24, last three lines) represents "intended use" language and thus is not afforded any patentable weight. Claims directed to apparatus must be distinguished from the prior art in terms of structure rather than function (e.g., see *In re Danly*, 263 F.2d 844, 847, 120 USPQ 528, 531 (CCPA 1959). "[A]pparatus claims cover what a device is, not what a device does." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990). (emphasis in original). A claim containing a "recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art apparatus" if the prior art apparatus teaches all the structural limitations of the claim. Ex parte Masham, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicant's claim language only sets forth what the apparatus does (i.e., adapted to visualize movements of molecules ... using a single dye tracing (SDT) method) rather than what it is (i.e., describe a structural limitation) and, as a result, fails to distinguish the claimed apparatus from the prior art in terms of its structure. Furthermore, it is even if *assuming arguendo* this "adaptation" is to be afforded patentable weight, the Examiner contends that the metes and bounds of the claimed invention cannot be determined (e.g., see 35 U.S.C. § 112, second paragraph below).

For ***claim 25***, Schmidt et al. disclose the use of biological cells (e.g., see Schmidt et al., page 2929, Conclusion).

For ***claims 26-27***, a recitation directed to the manner in which a claimed apparatus is intended to be used does not distinguish the claimed apparatus from the prior art – if the prior art has the capability to so perform. See MPEP 2114 and *Ex parte Masham*, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicants use of equal or different markers does not impart any patentably distinct features on the apparatus and thus is not given any patentable weight in accordance with MPEP § 2114. However, even if assuming arguendo the use of said sample markers were to be given patentable weight, Schmidt et al. disclose both equal and different marker molecules (e.g., Materials and Methods section wherein equal TRITC DHPE molecules are disclosed; see also bell curve in figure 2 showing some "markers" with less than 100 counts and some with greater than 300 counts i.e., different markers; see also Conclusion wherein different markers are disclosed).

For ***claim 28***, Schmidt et al. disclose the coordination and synchronization of 5 ms Gaussian-shaped laser beam pulses of 6.1 μm width and 57 kW/cm2 mean excitation intensity taken at 35 ms intervals (e.g., see figures 1 and 3).

For ***claim 30***, Schmidt et al. do not explicitly state that their laser will excite a range from 100 to 10,000 μm^2, but the Examiner contends that this level of excitation would be an inherent property of the laser because Applicants' most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see specification, page 7, middle paragraph, "only the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser"; see also claim 32) (emphasis added). "When the PTO shows a sound basis for believing that the products of

the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

For ***claim 31***, Schmidt et al. disclose positioning and shifting of images using a "frameshift" CCD camera equipped with both (1) acquisition and (2) storage functional capabilities and the ability to "synchronize" and "coordinate" between these two functions.

For ***claims 32 and 34***, Schmidt et al. disclose an argon-ion laser (e.g., see Schmidt et al., page 2926, column 1, paragraph 1).

For ***claim 33***, Schmidt et al. disclose an acousto-optically switchable laser light (e.g., see Schmidt et al., page 2927, column 1, paragraph 1, "The camera provided trigger pulses for the acoustoptic modulator for repeated illuminations").

For ***claim 35***, Schmidt et al. disclose a pulse transmitter and mechanism for controlling said transmitter wherein the laser can generate 5 ms pulses (e.g., see Schmidt et al., Materials and Methods section; see also page 2927, column 1, paragraph 1, "The camera provided trigger pulses for the acoustoptic modulator for repeated illuminations").

For ***claim 36***, Schmidt et al., disclose both "continuous" and "frameshift" CCD modes (e.g., see Schmidt et al., page 2926, column 2, last paragraph).

For ***claim 37***, Schmidt et al., disclose an epifluorescence microscope (e.g., see page 2926, column 1, last paragraph, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"; see also Materials and Methods section).

For ***claim 38***, Schmidt et al. disclose and efficiency of 3% (e.g., see Schmidt et al., page 2926, column 1, last paragraph).

For ***claim 39***, Schmidt et al. disclose a N_2 cooled CCD camera with a large pixel array and noise of only a few electrons per pixel (e.g., see page 2926, column 1, last paragraph, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"; see also Materials and Methods section wherein 4 counts/pixel read-out noise is disclosed). Schmidt et al. do not disclose the quantum efficiency or dark counts of their SDT system. The reference is silent on the issue. However, the Examiner contends that these features would be an inherent property of the system as disclosed by a later paper by Schmidt et al. (referred to herein as "Schmidt 1997") referring back to the previous studies (e.g., see Schmidt 1997, translation, page 7, Figure 1B shows the setup for single molecule detection with a conventional epifluorescence microscope and a nitrogen-cooled CCD camera (4cnts readout noise, dark counts negligible, quantum efficiency 0.8 electrons/photon)"; please note that reference [12] refers to the previous Schmidt et al. article published in 1996).

For ***claim 45***, Schmidt et al discloses the same Axiovert 135-TV Zeiss microscope as that disclose in Applicant's preferred embodiments (e.g., see Example 1 in Specification) and, as a result, must possess the same parallel beam region. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

The prior art teachings of Schmidt et al. differ from the claimed invention as follows:

For ***claims 29 and 35***, Schmidt et al. are deficient in that they do not specifically teach the use of an XYZ stage for automated lateral and vertical movements. Schmidt et al. is silent on the issue.

For ***claim 40***, Schmidt et al. are deficient in that they do not teach the use of a pixel array > 1340 × 1300.

For ***claim 42***, Schmidt et al. are deficient in that they do not teach the use of a microtiter plate.

For ***claim 44***, Schmidt et al. are deficient in that they do not teach the use of a piezo element used in conjunction with the XYZ stage for Z moments.

However, the combined references of Lewis et al., Al-Ghoul et al. and Albertine et al. teach the following limitations that are deficient in Schmidt et al.:

For ***claims 29 and 35***, Lewis et al. (see entire document) teach that x, y and z control using an automated flat scanning stage (e.g., see Lewis et al., Summary of the Invention; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously"; see also figures 1-4).

For ***claim 40***, Al-Ghoul et al. teach the use of a pixel array that is 2048 × 2048 (e.g., see page 2, column 2, paragraph 2).

For ***claim 42***, Albertine et al. teach the use of a microtiter plate for use in microscopy of biological samples for "parallel" screening and identification (e.g., see Albertine et al., abstract).

For ***claim 44***, Lewis et al. teach the use of a piezo element (e.g., see Lewis et al., Summary of the Invention; see also figures 1, 2 and 4; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously").

It would have been obvious to one skilled in the art at the time the invention was made to use the single dye tracing apparatus as taught by Schmidt et al. with the automated flat scanning XYZ stage as taught by Lewis et al. because Lewis et al. explicitly states that their "flat design" is "particularly well suited for ... microscopy" (e.g., see Lewis et al., column 1, lines 11-14), which would encompass the confocal microscopy apparatus disclosed by Schmidt et al. (e.g., see Schmidt et al., Introduction).

Furthermore, one of ordinary skill in the art would have been motivated to use the piezo XYZ stage disclosed by Lewis et al. because Lewis et al. explicitly state, "The principle advantage of the present scanner over previous geometries is that the three-dimensional scanning is accomplished in a flat thin plate which can be readily placed close to a high power microscope objective" (e.g., see Lewis et al., column 2, lines 40-45; see also paragraph bridging columns 3-4), which would encompass the microscope objective disclosed by Schmidt et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Lewis et al. teach that their stage is compatible with all types of microscopes (see Lewis et al., Summary of Invention; see also column 4, paragraph 1, "Since the scanner does not extend below the plane of the plate, the objective is completely free to be exchanged by the simple rotation mechanisms found in all optical microscopes").

In addition, a person of skill in the art would have been motivated to use the microtiter plates disclosed by Albertine et al. with the single dye tracing apparatus as disclosed by Schmidt et al. because Albertine et al. explicitly states that their microtiter plates can be used with microscopy (e.g., see Albertine et al., abstract). Furthermore, a person of skill in the art would have been motivated to use a microtiter plate to prepare and/or test samples in "parallel" i.e., to save time. Furthermore, a person of skill in the art would have reasonably been expected to be successful because Albertine et al. show that microtiter plates can be used in conjunction with microscopes.

Finally, a person of skill in the art would have been motivated to use the 2048 × 2048 pixel array to replace the smaller arrays disclosed by Schmidt et al. because this

array is designed to collect images in the same manner as the smaller arrays (i.e., the references represent analogous art). A person of skill in the art would have been motivated to use the array disclosed by Al-Ghoul et al. because it possesses higher resolution (i.e., 2048 × 2048). A person of skill would have reasonably been expected to be successful because the array is used in a CCD camera just as is the case for Schmidt et al.

Response

17. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicant argues, "Schmidt does not teach the visualization of movements of molecules, interactions between molecules, and molecular processes with a three-dimensional biological cells or cells" (e.g., see 6/27/05 Response, pages 16-17, especially page 17, paragraph 1).

[2] Applicant argues, "... nowhere does Schmidt teach 'a control unit adapted to coordinate and synchronize ... lateral movement between said sample holder and said detection system, ' nor does Schmidt teach 'at least one of the sample holder and the detection and analysis system is movable laterally, relative to the other during use.' (e.g., see 6/27/05 Response, page 17, last full paragraph).

[3] Applicant argues, "Neither Schmidt nor any of the secondary references teaches or suggests each element of claim 24 ... therefore claim 24 is not obvious and must be patentable" (e.g., 6/27/05 Response, pages 17-18).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. Schmidt does teach the visualization of movements of molecules and the interactions between those molecules (e.g., see Schmidt et al., abstract, "Here we provide methodology for visualization of the motion of individual fluorescent molecules"; see also figures 1 and 3 showing interaction of individual lipid with other lipids in the membrane; see also newly amended rejection above; see also 35 U.S.C. § 112, second paragraph rejection below, which is incorporated in its entirety herein by reference).

In addition, In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "three-dimensional biological cell or cells") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

[2] In response to applicant's arguments against the Schmidt et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined references teach all of the claimed limitations (e.g., see newly amended rejection above; see also Lewis et al., column 3, lines 24-28; see also figure 1-4).

[3] Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 24-40, 42, 44, 45 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 24**, the phrase "wherein the arrangement is adapted to visualize movements of molecules ... by using the single dye tracing (SDT) method" is vague and indefinite. For example, the claimed recitation of a use (i.e., "use" of the SDT method), without setting forth any steps involved in the process (i.e., no positive method steps are set forth for the SDT method in the claim), results in an improper definition of a process (e.g., see for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966)) and, as a result, an improper definition of the apparatus that is defined (in part) by said process. Furthermore, it would appear that all of the recited elements (e.g., source of light, sample holder, etc.) could be used to monitor the movement of molecules, interactions between

molecules, etc. without such an adaptation (e.g., see claim 1 of PCT/AT99/00257 priority document wherein no such "adaptation" is required for "visualizing molecules, movements thereof, and interactions between molecules, and molecular processes in a sample, in particular molecules and processes in biological cells, by using the single dye tracing"; see also specification pages 6-7). Thus, it is not clear what adaptation would be required when Applicant's priority document and specification states that no such adaptation is required.

In addition, the Schmidt et al. reference (Schmidt, T. H.; Schutz, G. J.; Baumgartner, W.; Gruber, H. J.; Schindler, H. "Imaging of single molecule diffusion" PNAS 1996, 93, 2926-2929) used in the 35 U.S.C. § 103(a) rejection above, according to Applicant, teaches at least one variation of the currently claimed "single dye tracing" method (e.g., see Schmidt, T. H.; Hinterdorfer, P.; Schindler, H. "Microscopy for Recognition of Individual Biomolecules" Microscopy Research and Technique **1999**, 44, 339-346, page 339, column 2, "(SDT) permits the detection and imaging of the mobility of individual biomolecules on biological membranes ... Schmidt et al. (1996a) [i.e., Applicant references the above PNAS article, used in the 35 U.S.C. §103(a) rejection as an example of an SDT method]"). However, Applicant also states that this SDT method does not lead to the currently claimed "visualization of movements of molecules ..." (e.g., 6/27/05 Response, page 17, paragraph 1, "Schmidt [i.e., the PNAS reference above] does not teach the visualization of movements of molecules ..."). Thus, it is also unclear how the SDT method can be "used" to adapt the currently claimed arrangement for the "visualization of molecules ..." when Applicant expressly acknowledges that the SDT

methods does not lead to such a result. Therefore, claim 24 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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October 6, 2005

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